

Immunomodulatory and Kidney-Protective Effects of the Human Chorionic Gonadotropin Derivate EA-230

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Abstract

The systemic inflammatory response following infectious or non-infectious insults is related to morbidity (including acute kidney injury) and mortality. Pregnancy is associated with immunotolerance and an increased glomerular filtration rate. EA-230, a linear tetrapeptide (Alanine-Glutamine-Glycine-Valine), derived from the β -chain of the human chorionic gonadotropin hormone, has shown immunomodulatory and renoprotective properties in several pre-clinical animal models of systemic inflammation. Furthermore, an excellent safety profile of EA-230 was observed in phase 1 studies in humans, and the immunomodulatory effects of EA-230 were recently demonstrated in a phase IIa study during human experimental endotoxemia. A prospective double-blind placebo-controlled randomized trial in 180 patients undergoing elective CABG-surgery with or without valve surgery is currently conducted to investigate the immunomodulatory and renoprotective properties of EA-230.

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Introduction

Infectious (e.g., sepsis) and non-infectious conditions (e.g., trauma or major surgical interventions) activate the innate immune system, resulting in a systemic inflammatory response. This activation of the immune system is essential for clearance of pathogens and initiation of tissue repair. However, a too persistent or overwhelming inflammatory response can be detrimental, as it may lead to tissue damage and organ dysfunction with associated mortality rates up to 30% [1].

Development of acute kidney injury (AKI) is one of the first and most frequent manifestations of organ failure in systemic inflammation-related conditions and occurs in over a half of critically ill patients [2]. AKI has been as-

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sociated with impaired clinical outcome and mortality; even a minimal increase in serum creatinine has been shown to correlate with impaired survival in patients undergoing elective cardiac surgery [2, 3].

It is increasingly recognized that inflammation plays a key role in the pathogenesis of AKI. This is for instance illustrated by associations between plasma levels of key inflammatory mediators, such as interleukin (IL)-6, and the development of AKI and mortality following cardiac surgery [4] and sepsis [5]. Despite the impact of systemic inflammation and the associated development of AKI, no immunomodulatory interventions have proven to be effective in regulating the systemic inflammatory response to prevent organ damage. Clearly, novel therapeutic strategies are warranted.

What Can We Learn from Pregnancy in the Search for New Immunomodulatory Therapies?

Pregnancy is an improbable symbiosis of 2 major histocompatibility complex-incompatible individuals. The adaptation of the maternal immune system during pregnancy has sparked research into new immunomodulatory strategies. This is based on the fact that pregnancy represents a unique immunologic situation in which the maternal immune system is adapted to tolerate the semi-allogeneic foetus, while maintaining the capacity to clear invading pathogens. Interestingly, the attenuated disease activity of various auto-immune diseases like rheumatoid arthritis and multiple sclerosis during pregnancy represents another hallmark of this immune-tolerant anti-inflammatory phenotype, underscored by the fact that these diseases often relapse following delivery [6]. These features are suggestive of specific modulation of the immune system in such a way that harmful immune processes to mother and foetus are suppressed, while beneficial immune processes remain unaffected. If a pharmacological compound could mimic these effects, immune suppression without the increased susceptibility for infections would be possible.

β -Human Chorionic Gonadotropin-Derived Immunoactive Oligopeptides

In the last decades, several theories have been postulated concerning the exact mechanisms behind the pregnancy-associated immune-tolerant phenotype. Of these,

the hormonal milieu and, in particular, the release of human chorionic gonadotropin (hCG), is believed to play a pivotal role. hCG is present already at a very early stage, is produced throughout pregnancy and has been shown to exert immunomodulatory effects [7]. This has led to the discovery of immunologically active fragments originating from the β -loop of hCG, which are abundantly present during pregnancy [8]. Recent studies in animal models of systemic inflammation showed that these oligopeptides exert immunomodulatory properties and limit organ failure and mortality [8–11]. Of particular interest is the linear tetrapeptide Alanine-Glutamine-Glycine-Valine, later coined EA-230, which showed high efficacy in terms of beneficial effects [8, 10, 12]. EA-230 prevented mortality in endotoxemic mice both when administered early (2 h) and late (24 h) after endotoxin administration [10]. Furthermore, a cocktail of 3 oligopeptides including EA-230 reduced the severity of sepsis induced by infusion of live *E. coli* in rhesus monkeys [10]. EA-230 also mitigated the release of inflammatory mediators, preserved renal function and improved survival in murine models of renal ischaemia-reperfusion and kidney transplantation [12, 13]. Finally, EA-230 prevented the release of systemic inflammatory mediators, attenuated tissue neutrophil infiltration, and reduced organ damage in haemorrhagic shock-induced systemic inflammation in mice [9]. Because of these promising results, EA-230 was advanced into clinical development.

Clinical Studies with EA-230

A recent phase I safety study in healthy volunteers revealed that intravenous administration of EA-230 is well tolerated and has an excellent safety profile [14]. A phase IIa study was subsequently conducted during experimental human endotoxemia, a human in vivo model of controlled systemic inflammation elicited by the administration of a low dose of *E. coli* endotoxin. In this study, subjects were treated with escalating doses of EA-230 (15, 45, 90 mg/kg/h) or placebo for 2 h. Administration of the highest dose of EA-230 resulted in reduced levels of pro-inflammatory mediators (IL-6 and IL-8, among others), significantly less flu-like symptoms and attenuated development of fever compared to placebo-treated subjects [14].

The structure of EA-230 and a summary of its effects in previous pre(clinical) studies is provided in Figure 1.

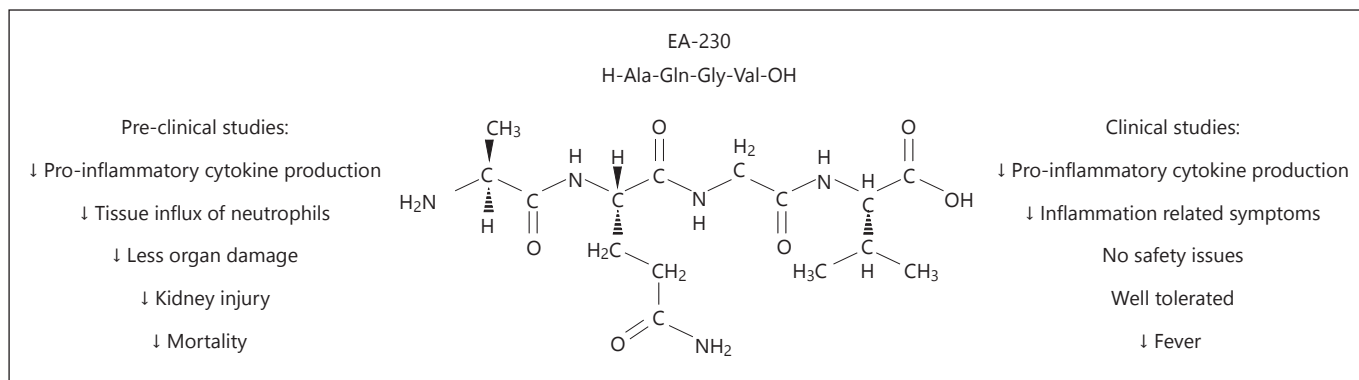


Fig. 1. Structure of EA-230 and summary of its effects as reported in previous pre(clinical) studies.

Future Directions

A clinical study is now warranted to investigate whether EA-230 also modulates the systemic inflammatory response in patients, to explore whether this is beneficial in terms of organ (kidney) function, and to confirm the safety profile obtained in animals and healthy volunteers. Elective surgery patients represent an ideal patient group to investigate the putative beneficial effects of EA-230, as the compound can be administered during the period that the inflammatory response and the insult to the kidneys occur. In addition, cardiac surgery patients represent a relatively homogeneous group, which displays a clinically relevant and reproducible inflammatory response. Therefore, a double-blind, randomized, placebo-controlled phase II trial is currently being conducted with EA-230 in patients undergoing elective cardiac surgery using cardiopulmonary bypass (www.clinicaltrials.gov; NCT03145220). One hundred and eighty patients will be randomized to either 90 mg/kg/h EA-230 or placebo. Study drug infusion will be initiated upon the first incision made by the surgeon and will continue as long as the patient is on extracorporeal circulation. Serial blood samples will be drawn to determine inflammatory mediators. In addition, renal function (glomerular filtration rate) will be determined on the day prior to surgery and on the day after surgery using iohexol methodology [15]. Secondary endpoints include safety and pharmacokinetics, circulating inflammatory markers (IL-6, tumour necrosis factor- α , IL-8, IL-10, IL-1 receptor antagonist, monocyte chemoattractant protein-1, IL12p70, macrophage inflammatory protein [MIP]-1 α , MIP-1 β), renal injury determined by plasma levels and urinary excretion of tubular injury markers (including kidney injury marker-1, neutrophil gelatinase-associated lipocalin, fatty acid-

binding protein, tissue inhibitor metalloproteinase-2 and insulin-like growth factor binding protein-7, Proenkephalin) and clinical sequela (including fluid balance, vasopressor need, insulin-sensitivity and SOFA and SIRS scores). Patient enrolment and 90-day follow-up were recently completed and database lock will be performed in May 2018.

Conclusion

Systemic inflammation is a complex and dynamic process. An overwhelming or too persistent response can lead to tissue damage and organ failure, in which, particularly, the kidneys are affected. Treatments aiming to prevent AKI are warranted because kidney injury is correlated with mortality in critically ill patients. So far, therapeutic strategies have failed to improve outcome, and current therapy only consists of supportive treatment. β -hCG-derived oligopeptides have been shown to exert immunomodulatory effects associated with the preservation of kidney function and reduction of mortality in various preclinical studies. Immunomodulatory effects of EA-230, which is one of the oligopeptides displaying high efficacy, were recently confirmed in an experimental human endotoxemia trial. Currently, a large double blind placebo-controlled randomized phase II clinical trial is underway to evaluate EA-230's immunomodulatory and renoprotective effects in patients with systemic inflammation following cardiac surgery.

Disclosure Statement

The authors declare that they have no conflicts of interest to disclose.

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